Comment on "Worldwide Distribution of PK Deficiency: the Defect Seems Mainly Concentrated in West African Countries and the United States"

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Letter to the Editor

Comment on "Worldwide Distribution of PK Deficiency: the Defect Seems Mainly Concentrated in West African Countries and the United States".

Keywords: PK; Deficiency; West African Countries; United States.

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To the editor.

We read the recently published letter to the editor by Dr. Girolami and Dr. Ferrari.[1] While it does not add anything novel to our knowledge on severe prekallikrein (PK) deficiency, it misleadingly reported on recent works, which showed for the first time the much higher than the anticipated prevalence of severe PK deficiency among subjects of African origin.[2,3] Finally, Girolami and Ferrari cited multiple reviews of the literature characterized by inadequate methodology for systematic searches without, in contrast, citing the sole comprehensive analysis of the clinical, laboratory, and genetic characteristics of severe PK deficiency.[2] Furthermore, they discredited a follow-up paper as preliminary.[3]

In May 2020, we published a systematic study on severe PK deficiency,[2] the results of which had previously been presented at the American Society of Hematology Congress in December 2018.[4] Among other findings, including the demonstration that some *KLKB1* variants previously described in the literature as causal mutations for PK deficiency represented, in fact, benign polymorphisms, we reported two African patients from Ghana and Somalia, respectively, with the same homozygous *KLKB1* variant (c.451dupT, p.Ser151Phefs*34). This variant has not been noticed in the international literature so far, despite a minor allele frequency of 1.43% for African subjects, according to the large Genome Aggregation Database (gnomAD). This datum suggests that severe PK deficiency in Africans could be as common as 1/4725 general population just based on this unique mutation, which appears predominant in this ethnic group,[2] but is much less common in other groups. In a follow-up project intended to substantiate the high prevalence of the *KLKB1* c.451dupT mutation in African origin subjects,[3] we investigated 300 healthy Nigerians and confirmed a high allele frequency (7/600 alleles corresponding to 1.17%). In this manuscript, we provided a more detailed analysis of the variant's frequency also by looking at other genome databases, again confirming the high frequency in African populations of different origin (native African, African-American, and Afro-Caribbean).[3] In addition, in another severe PK deficient patient from Oman identified in,[2] we found out that he was also a homozygous carrier of c.451dupT,[3] and we identified another homozygous c.451dupT carrier from the literature,[5] which turned out to be American of African origin after personal communication with one of the authors (the ethnicity was not mentioned in the manuscript).

Based on the aforementioned elements, we conclude that Girolami and Ferrari's letter to the editor is, at least, misleading.[1] In particular, the sentence "defect present in 1.27% of 300 Nigerians" is at the same time imprecise (it is unclear whether they refer to the minor allele frequency or the prevalence of severe PK deficiency) and incorrect (in our manuscript, a value of 1.17% was reported). Moreover, and as detailed above, this published data is far more than "preliminary", having been confirmed using data from different cohorts and databases.[2,3] It comes indeed as a surprise that this evidence has then been embraced by Drs. Girolami and Ferrari without citing the original works correctly[2] or, as it is the case in a brief more recent communication from the same authors on the same topic, not citing them at all.[6]

Finally, and beyond the discussion on the actual prevalence of severe PK deficiency, we believe that our estimates of bleeding and cardiovascular risks[2] represent the most reliable figures available in the literature. Reasons for that are that (i) these are provided both as age-stratified and depending on individual follow-up time, (ii) prior analyses erroneously presented duplicated data from different reports of the same case, (iii) the process of the systematic review was conducted with adequate and transparent methodology, also

covering the grey literature and describing each step of study selection in great detail.[2]

Multinational cooperation involving global coagulation experts is being set up to conduct the first international registry on severe PK deficiency and answer open questions on this condition.

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